PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
GIULIO A. DECONTI
LAHIVE & COCKFIELD, LLP
28 STATE STREET
BOSTON, MA 02109

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	22 JUN 2006
Applicant's or agent's file reference HUI-054PC	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/44095	20 December 2004 (20.12.2004)	18 December 2003 (18.12.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC: C12N 9/10(2006.01),5/00(2006.01);A61K 38/16(2006.01),C07H 21/04
USPC: 435/193,37;530/358;536/24,5

Applicant

PRESIDENT AND FELLOWS OF HARVARD COLLEGE

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	10 May 2006 (10.05.2006)	Ponnathapura Achutamurthy Telephone No. (571) 272-0928

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/44095

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/44095

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. _____

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/44095

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-66	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-14, 16, 19-45 and 47-66	YES
	Claims 15, 17, 18, 46	NO
Industrial applicability (IA)	Claims 1-66	YES
	Claims None	NO

2. Citations and explanations:

Claim 15, 17 and 18, are lacking an inventive step under PCT Article 33(3) as being obvious over US 6,090,561 patent that teaches a method for identifying a compound that modulates interaction between NIP45 and NFAT, and a method for identifying a compound that modulates the activity of NIP45; see claims 8 and 13. The patent teaches also methods for modulating production of Th2 -associated cytokine, in particular IL-4, wherein the activity of NIP45 is modulated; see the abstract.

Claim 46 is lacking an inventive step under PCT Article 33(3) as being obvious over US 5,858,711 ('711) in view of 6,090,561 (561). '711 teaches a method for identifying a compound that modulates activity of NIP45 by determining the level of expression of the reporter gene in a cell transformed to express NIP45. '561 patent teaches modulating production of Th2 -associated cytokine, in particular IL-4, wherein the activity of NIP45 is modulated. In view of '561 teaching it would be obvious to use a method for modulating production of a cytokine wherein the method comprises the method of identifying a modulator of NIP45 activity as taught in '711.

Claim 1-14, 16, 19-45, and 47-66 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest that PRMT1 is the enzyme that methylates specifically NIP45 rendering it active.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/44095

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/44095

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

VIII. The following observations on the clarity of the claims, description, and drawings or on the questions, are made:
Claims 13, 20, 31, 33, 59, and 62 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 13, 20, 31, 33, 59, and 62 are indefinite for the following reason(s):

Claims 13 is directed to a method for identifying a compound that modulates cytokine production wherein that compound is identified by measuring cytokine production.
Claim 20 recites a polypeptide comprising amino acids 1-32 of NIP45, but amino acids 1-32 of NIP45 do not act as NIP45, i.e., a polypeptide comprising them does not have a NIP45 activity unless it is a NIP45.
Claim 31 lacks antecedent for "the test compound".
Claaim 33 recites in part b) "interaction between the NIP45 and", however the indicator of part "a) does not comprise the NIP45, only amino acids 1-12, that do not act as NIP45.
Claim 59 is unclear because it seems to be directed to a method of modulating IL-4 production and not IL-4 itself.
Claims 62 recites "contacting an immune cell" but it is not clear whether the contacting is in a treated subject of ex vivo.

Claims 2, 4, 15,16, 17, 20, 30, 30, 33, 37, 39, are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claim 2, 4, 15,16, 17, 20, 30, 30, 33, 37, 39 are not fully supported by the description. The application, as originally filed, did not describe:

Claim 2 does not describe which T-cell receptor signaling is to be modulated.
Claim 4 is lacking description of the upstream regulatory regions controlling expression of PRMT1.
Claims 15,15,17 are lacking description of the method for selecting a compound that modulates the activity of NIP45.
Claims 20 and 33 are lacking description of structure of a polypeptide that comprises amino acids 1-32 of NIP45 and acts as NIP45. In addition claim 33 lacks description of PRMT polypeptide.

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Claim 37 lacks description of gene whose transcription is to be modulated.
Claim 39 is objected as lacking support for a library of small molecules.

Claims 1, 2, 3, 4, 20, 42, 48, 50 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claim 1, 2, 3, 4, 20, 42, 48, 50 are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because

The person skilled in the art cannot carry out the claimed invention without knowing which cytokine production is to be modified - the specification teaches modification of production of IL-4 and IF-γ; which signaling is to be modified; what are the structures of the upstream regulatory regions controlling expressing PRMT1; how to make a polypeptide comprising amino acids 1-32 ofNIP45 and acting as NIP45.

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